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DIGESTIVE DISEASES

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NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

DIGESTIVE DISEASES

Digestive diseases such as peptic ulcers, gallstones, and liver diseases are a major health problem in the United States today. Twenty million Americans are treated for some type of chronic digestive disorder each year, and according to the National Digestive Diseases Advisory Board, almost half the U.S. population suffers an occasional digestive disorder.

Economically, digestive diseases also take a significant toll. Direct medical costs alone total $17 billion each year. In fact, more Americans are hospitalized due to diseases of the digestive tract than for any other group of disorders. Some 200,000 people miss work each day because of digestive problems, resulting in current costs of $50 billion a year in lost wages, reduced productivity, health care expenditures, and disability payments.

Although digestive diseases cause approximately 200,000 deaths annually, the actual count may be much higher, because digestive diseases are often underlying causes of death that do not appear in official statistics.

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) supports research into the causes, prevention, diagnosis, and treatment of digestive diseases such as peptic ulcers, diverticulitis, infectious diarrhea, inflammatory bowel disease, gallstones and gallbladder disease, cirrhosis, esophagitis, and malabsorption syndromes. The known causes of digestive diseases range from infections, metabolic disorders, or genetic defects to neuromuscular disorders, toxins, and reactions to stress.

Through the Institute's intramural research program and the awarding of extramural grants to scientists at universities and medical centers around the country, exciting research advances have been made in digestive disorders.

Gallstones

An estimated 25 million Americans suffer from gallstone disease, a common medical problem that costs the American public $1 billion in surgical expenses annually. Each year, about 1 million new cases of gallstones are discovered. Although new medical techniques have been developed to dissolve gallstones in some patients, none of these methods can consistently prevent a recurrence of the problem.

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Progress is being made in understanding the process of gallstone formation. NIADDK grantees Dr. Martin Carey of the Brigham and Women's Hospital in Boston and Dr. John Lamont of the Boston University Medical Center found abnormally high levels of a protein in the mucous secretion from an animal gallbladder prior to stone formation. In another study, Dr. Lamont and NIADDK grantee Dr. Roger Soloway of the University of Pennsylvania found high concentrations of this same protein in human gallstones. These findings demonstrate a possible causal relationship between abnormal mucous protein secretion and subsequent gallstone formation.

In related work, NIADDK grantee Dr. Thomas Holzbach and his colleagues at the Cleveland Clinic Foundation have shown that gallbladder bile contains a protein that helps to prevent stones from crystallizing.

The researchers suggest that gallstone formation may result either from a deficiency of the inhibiting protein or from large amounts of the mucous protein sufficient to cancel the effect of the inhibiting protein. The development of a successful method for slowing mucous protein secretion may lead to an effective treatment for preventing gallstones in high risk groups.

Peptic Ulcers

Approximately 4 million Americans have ulcers of the stomach and duodenum, and over 7,000 people die each year from ulcers or complications associated with them.

Stomach Cell Physiology

Using animal models, NIADDK grantees Drs. Susumu Ito and Michael Rutten of Harvard University and Dr. William Silen of the Beth Israel Hospital in Boston have been studying how the stomach can repair itself after damage inflicted by different types of noxious chemicals. Aspirin is a chemical compound that has long been known to cause ulcers in arthritis patients taking large doses of this anti-inflammatory agent. NIADDK grantee Dr. Gordon Kauffman of the University of California at Los Angeles has found that aspirin has different effects on the stomach depending on the method of administration and dosage. These findings may help scientists to understand how aspirin causes ulcers and how to induce the injured stomach to repair itself.

New Ulcer Drugs Tested

NIADDK intramural scientists Drs. Katherine McArthur, Martin Collen, Jay Cherner, John Howard, Paul Maton, Robert Jensen, and Jerry Gardner have compared the effectiveness of two new drugs--famotidine and omeprazole--for the treatment of ulcers to cimetidine and ranitidine, the two most popular drugs currently prescribed for ulcer patients.

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The researchers found that famotidine was 10 to 35 times more potent in protecting the lining of the stomach than either cimetidine or ranitidine, and that patients given famotidine for up to 7 months showed no adverse side effects. However, like cimetidine and ranitidine, famotidine must be taken several times a day to be effective.

In a second study, the scientists treated eight patients with a single daily dose of omeprazole for 6 months. This drug successfully inhibited stomach acid secretion and caused no observable side effects. Omeprazole holds hope for long-term treatment of Zollinger-Ellison syndrome, a condition marked by severe recurrent ulcers due to the production of several times the normal amounts of stomach acid.

Liver Diseases

The liver performs many complex biochemical tasks. As the largest internal organ in the human body, the liver functions as a "chemical factory." It purifies and detoxifies blood, stores certain nutrients, produces a variety of blood proteins, and secretes fluids such as bile that aid in digestion and waste removal. Because of its many functions, the liver is particularly vulnerable to many types of disease. In fact, each year over 25,000 Americans die from chronic liver disorders.

A significant advance that may help scientists better understand the processes of liver and biliary diseases has been made by NIADDK grantees Drs. James Boyer and Gerhard Giebisch of Yale University in New Haven, Connecticut. Using minute instruments, these investigators have been able to pierce the wall of cells that surround the canaliculus--the small tubule where the process of bile secretion in the liver begins--and enter this tubule for the first time. This achievement is important because it will allow researchers to follow the process of bile secretion and to document changes that occur in the bile as it flows to the gallbladder for storage.

Liver Transplantation

In February 1984 NIADDK grantee Dr. Thomas E. Starzl and his colleagues from the University of Pittsburgh Health Center successfully transplanted both a heart and a liver into a 6-year-old girl with familial hypercholesterolemia. This is a rare genetic disorder marked by a defect in the metabolism of low density lipoproteins (LDL), which are among the primary carriers of cholesterol in the body. The disease causes a buildup of cholesterol in the blood vessels throughout the body and usually results in an early death from heart attack.

LDL receptors, particularly those in liver cells, play an important role in the breakdown of cholesterol in the body. Recent research has shown that in healthy individuals approximately 75 percent of these receptors are located in the liver. However,

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patients with hypercholesterolemia lack LDL receptors. By replacing the damaged heart and the diseased liver with healthy organs from a donor child, the scientists were able to give the patient the 75 percent of LDL receptors normally located in the liver and reduce the patient's blood cholesterol levels.

Inflammatory Bowel Disease

Both Crohn's disease and ulcerative colitis are chronic inflammatory disorders of unknown cause that affect the intestinal tract and can result in diarrhea, abdominal pain, blood in the stool, and fever. An estimated 2 million Americans suffer from one or the other of these inflammatory bowel diseases (IBD). Although certain drugs can control the symptoms of Crohn's disease and ulcerative colitis, there is no known cure for either of these serious disorders.

Recent research into the cause of inflammatory bowel disease has focused on various agents that might induce inflammation or set off an autoimmune response in which the body attacks its own intestinal tract as if it were a foreign substance.

NIADDK grantee Dr. Claudio Fiocchi and his colleagues at the Cleveland Clinic Foundation examined the intestinal lining of a group of patients with IBD. The scientists found that all of the subjects exhibited abnormally low levels of interleukin-2, a protein required for proper immune system function. The researchers suggest that a deficiency of this protein may induce an immune system response leading to the inflammatory reaction seen in Crohn's disease and ulcerative colitis.

In another study of intestinal tissue of IBD patients, NIADDK grantee Dr. William Stenson of the Washington University School of Medicine in St. Louis, Missouri, found higher than normal levels of leukotriene B4, a chemical agent that attracts defensive white blood cells called neutrophils. Because white blood cells are associated with an inflammatory reaction, the finding suggests that leukotriene B4 may be an important mediator of inflammation in IBD.

Marmoset Monkey as a Model for IBD Research

In a 3-day workshop cosponsored by NIADDK, experts in gastroenterology, oncology, nutrition, animal care, and immunology met at the Oak Ridge Associated Universities in Oak Ridge, Tenn., to discuss the suitability of using the marmoset monkey as a laboratory model for studying ulcerative colitis and subsequent colon cancer. The medical group determined that the marmoset may offer new hope for understanding the disease process of ulcerative colitis in humans because it is one of the few animals that exhibits a natural tendency to develop a similar disorder. The scientists also said it is important to note that, as an endangered species, the marmoset itself can benefit from any advances made in future laboratory research.

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Malabsorption Syndromes

Two Genes May Be Responsible for Gluten Intolerance

Gluten-sensitive enteropathy (GSE), also known as gluten intolerance or celiac sprue, is a disorder marked by a malabsorption of nutrients in the small intestine. People with this condition have an intolerance to gluten, a protein commonly found in wheat, rye, and other types of grain products. According to the American Celiac Society, over 98,000 U.S. citizens suffer from GSE. Because gluten is present in many foods including soups, ice cream, breads, and hot dogs, GSE patients who are being treated by a gluten-free regimen must adhere to a restricted and rigid diet that excludes such substances.

GSE is an hereditary disease. Until now, its onset was attributed to the presence of a single genetic marker. However, many people that have the genetic code for gluten sensitivity do not develop the disorder. Dr. Martin Kagnoff, an NIADDK grantee at the University of California at San Diego, and his colleagues there have examined the genetic control of GSE in mice. Their studies revealed that not one but two separate genetic markers may be responsible for the occurrence of GSE. They have found similar results in preliminary studies of human GSE. These findings may explain why many children of GSE patients surprisingly do not exhibit an intolerance to gluten.

Yogurt Digested by Lactose-Intolerant People

An estimated 50 million adult Americans are unable to digest milk and dairy products because of a condition known as lactose intolerance. These people have a deficiency of the enzyme lactase, which breaks down lactose, the sugar in milk. If dairy products or foods containing milk are ingested, abdominal pain, gas, and diarrhea can result.

NIADDK grantee Dr. Michael Levitt and his associates at the University of Minnesota in Minneapolis reported that yogurt is a suitable source of milk for lactose-intolerant people. The investigators found that small amounts of lactase are present in yogurt. When ingested, the yogurt gives a lactase deficient person a temporary increase in the supply of this enzyme. The catalytic activity of the lactase allows the patient to break down the lactose in the yogurt and avoid the characteristic symptoms of lactase deficiency.

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National Cancer Institute

New cases of cancers of the digestive organs will total 207,000 in 1984, with 117,300 deaths, according to estimates of the American Cancer Society based on 1973-1979 data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program.

According to 1984 estimates, new cases of cancer of the colon (90,000) and rectum (40,000) account for 62 percent of all cancers of the digestive system. Deaths from cancers of the colon and rectum are estimated to be 59,400, or 51 percent of digestive system cancer deaths.

In men, colon and rectum cancers combined have the third highest incidence (62,000), following lung cancer and prostate cancer. However, in estimates of cancer deaths, colorectal cancer moves up to second place for men at 28,800. For women, colorectal cancer incidence totals 68,000, second only to breast cancer, and drops to third place, after breast and lung cancers, in estimates of cancer deaths at 30,600.

In the past, imaging of tumors using radiolabeled antibodies has required computer-assisted subtraction techniques to reduce background activity. Now, NCI grantees have developed a method that ultimately may improve radioimmunodetection of cancer and may also be applicable to antibody-mediated therapy.

Drs. Robert M. Sharkey, F. James Primus, and David M. Goldenberg of the University of Medicine and Dentistry of New Jersey in Newark, and the University of Kentucky Medical Center in Lexington, found that administering a second antibody may improve tumor imaging with a radiolabeled antitumor antibody. Hamsters that had received grafts of human colon tumors were given a radiolabeled antibody to carcinoembryonic antigen (CEA), a marker in blood that may indicate the presence of colon or other cancers. The researchers then gave the hamsters a second antibody directed against the CEA antibody. This resulted in a decrease in the background level of radioactivity in the hamsters' blood.

Flow cytometry is a relatively new diagnostic technique in which a laser hooked to a computer is used to analyze cells that had been labeled with fluorescent markers. At Memorial Hospital for Cancer and Allied Diseases in New York, NCI grantee Dr. Myron R. Melamed is using flow cytometry techniques developed in his laboratory and elsewhere to analyze changes in nucleic acid content, chromatin structure and protein from normal colon tissues, inflammatory and abnormal polyps, and primary and metastatic cancer. He hopes to identify features of prognostic importance. These studies are expected to yield biochemical and functional information about the colonic cells that cannot be

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obtained in any other way. They provide a powerful new tool for quantitatively examining colonic tumors--valuable for prognosis and monitoring drug treatment effects--and also yield basic information on changes in DNA, cell cycle kinetics (rates of change), RNA and proteins during carcinogenesis.

Within the past year several investigators have succeeded in synthesizing an important mutagen--a substance that alters genetic material--isolated from the feces of apparently healthy persons. (During 1983 the mutagen's chemical structure and production in the intestine by bacteria that live without oxygen were established by NCI grantees Drs. Tracy D. Wilkins and Roger Van Tassell and colleagues at the Virginia Polytechnic Institute, State University, Blacksburg.) Three different approaches to this synthesis have been taken in 1984 by (1) Drs. Wilkins and Van Tassell; (2) Dr. Kyriacos Nicolaou, an NCI grantee at the University of Pennsylvania in Philadelphia; and (3) SRI in Menlo Park, California, a contractor working with NCI's intramural program. Through cooperation of the second and third group of investigators, sufficient quantity of the synthesized fecal mutagen is now available for NCI to supply it to biomedical scientists for research. More investigation is necessary to determine if this mutagen can cause cancer.

A case control study has begun to determine whether high mutagen levels are associated with colorectal cancer, and if so whether they can be affected by factors such as changes in diet. This intramural study is being conducted in cooperation with Walter Reed Army Medical Center and the Naval Medical Center in Bethesda departments of colorectal surgery. It is anticipated that 100 colorectal cancer patients and controls will be entered and the study completed within 2 years. Principal investigators are NCI's Drs. Gerald Batist and Mark Schiffman. Dr. Roger Shaw and A. W. Andrews at the Frederick Cancer Research Center, and Drs. Wilkins and Van Tassell at Virginia Polytechnic Institute are collaborating with the NCI investigators as laboratory contractors for this study.

Similar laboratory tests will be performed on material from a group of women participating in a study to evaluate the changes in biologic measurements associated with switching from a high-fat to a low-fat diet. This study is being conducted under an interagency agreement between NCI and the Department of Agriculture's facility in Beltsville, Maryland.

Emphasizing the possible significance of fecal mutagen research in relation to cause, and eventually to prevention, diagnosis, and treatment of colorectal cancer, NCI formed an in-house Task Force on Colon Cancer in 1984. It is co-chaired by Dr. Richard H. Adamson, director of the Division of Cancer Etiology, and Dr. Peter Greenwald, director of the Division of Cancer Prevention and Control.

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Primary liver cancer accounts for only 6 percent of all cancers of the digestive system in the United States. In 1984 there will be an estimated 13,300 cases and 10,100 deaths.

This cancer is rare in the West but very common in Asia and Africa. Risk of liver cancer appears to increase more rapidly with age than risk of colon cancer, stomach cancer, and lung cancer in nonsmokers. In smokers, the risk of liver cancer increases less rapidly with age than the risk of prostatic cancer and lung cancer.

A liver cancer study that has gained considerable attention is "Hepatoma Risk Evaluation and Early Detection with Alpha-fetoprotein (AFP)" conducted by Dr. R. Palmer Beasley, NCI grantee at the University of Washington, Seattle.

This large prospective study was begun in 1975 to determine (1) the incidence and relative risk of primary liver cancer among hepatitis B virus (HBV) carriers; and (2) the feasibility of annual AFP screening for the detection of early small removable tumors. The study population consists of 22,707 Chinese government employees in Taiwan. Fifteen percent of these employees carry HBsAg (hepatitis B surface antigen) in their blood, and primary liver cancer and/or cirrhosis is known to account for 20 percent of deaths within this basic population. (Of 71 cases of primary liver cancer, 70 have been among HBsAg carriers.) Investigators have obtained 95 percent adherence to annual followup for AFP testing and have enrolled 5,200 carriers in the screening program. AFP screening has more than 80 percent sensitivity and almost 100 percent specificity for primary liver cancer detection.

The investigators found that ultrasound is the most satisfactory method of identifying the precise location of the tumor. AFP screening has resulted in 52 patients being surgically treated. Thirty-nine of the 52 are still alive. Because 29 of the 52 resections were done within the past 2 years, the value of this surgery is still assessed with cautious optimism. Among the 23 patients on whom surgery was performed more than 2 years ago, 14 (61 percent) are still alive. Of the nine who died, four patients died during or as a result of surgery, and the other five due to tumor recurrence. Prior to AFP screening, the mortality from primary liver cancer was close to 100 percent within a year. Longer followup is necessary to learn whether these results are actually due to improved survival or represent the effect of early diagnosis.

Pancreatic cancer is a "silent" disease, without symptoms until it is advanced. Very little is known about what causes it or how to prevent it. It is usually fatal; only 4 percent of patients live more than 3 years after diagnosis. In 1984 in the United States there will be an estimated 25,100 new cases and 23,000 deaths. Within 5 years of diagnosis there is a 99 percent mortality.

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Progress has been reported by NCI grantees at the University of Iowa College of Medicine in Iowa City in pinpointing the cellular distributions of carcinogen-metabolizing enzymes within the part of the pancreas that secretes digestive enzymes. Dr. Jeffrey Baron and his colleagues are seeking to locate within pancreatic tissues the enzymes that help activate or deactivate chemical carcinogens. They have developed and used exquisitely sensitive and specific techniques to investigate the localization of particular cells and the distribution of these enzymes in the pancreas.

They are also using antibodies raised against a number of different carcinogen-metabolizing enzymes to localize these enzymes or related antigens in pancreatic tissues. They have a battery of different pancreatic cells they can follow sequentially for a variety of changes, and they can backtrack to identify the cells of origin for different lesions. So far, they have looked only at the rat pancreas. Accumulated evidence points to the acinar cell--a cell that lines small sac-like dilatations found particularly in glands such as the pancreas--as the cell of origin for exocrine pancreatic adenocarcinomas.

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National Institute of Dental Research

The National Institute of Dental Research (NIDR) sponsors research related to digestive diseases primarily through its studies of salivary glands.

The salivary glands are an integral part of the digestive system because they secrete digestive enzymes that convert starch and other macromolecules into smaller molecules. Like secretory tissues in other mucous membranes of the body, salivary glands also secrete immunoglobulins--proteins that can function as antibodies--that protect against infection. NIDR basic research includes investigations into the functional development and regulation of the salivary glands, the composition of saliva, and salivary gland secretions under normal conditions and in certain disease states such as Sjogren's syndrome and cystic fibrosis. Through these studies, insight will be gained into the mechanisms of secretion related to digestive diseases and the mechanisms of immune protection against mucous membrane infection.

Xerostomia, or dry mouth, is an area of particular interest to NIDR because a significant decrease in salivary flow or a change in the composition of saliva can have a profound effect on oral and dental health as well as nutritional status. Dry mouth is a symptom of certain disorders such as Sjogren's syndrome and is also a common side effect of numerous over-the-counter and prescription drugs and radiation therapy.

Drs. Bruce Baum and Philip Fox, NIDR intramural scientists, are continuing to screen patients with xerostomia through their dry mouth clinic. The researchers now have the ability to more accurately diagnose salivary gland dysfunctions and, in particular, to diagnose xerostomia caused by a malfunction of the salivary glands. This year the investigators began testing the use of a drug called pilocarpine for these cases. Given orally, pilocarpine is slowly absorbed into the body and induces saliva production by stimulating receptors on the surfaces of salivary gland cells. The drug shows great promise in restoring salivary gland function in certain cases.

The researchers also are collaborating with Dr. Barbara Sonies of the Clinical Center Rehabilitation Medicine Department and Dr. Thomas Shawker of the Diagnostic Radiology Department in related studies of xerostomic patients who have difficulty swallowing. This research team is the first to use an ultrasound imaging machine to diagnose swallowing disorders. With this approach, the investigators can accurately find the problem's cause so that effective therapies can be developed.

At Georgetown University, Washington, D.C., NIDR grantee Dr. Henry Mallek is studying patients with bulimia, an eating disorder characterized by recurrent episodes of binge eating followed by self-induced vomiting, which mainly affects young

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women of college age. He is examining the oral-pharyngeal tissues of bulimic patients to determine the incidence and severity of oral disease and salivary dysfunction. Medical complications of this disorder include gastritis, esophagitis, severe dehydration, and abnormal liver function. In addition, dental and oral-pharyngeal changes can occur as a result of the chemical and mechanical effects of vomiting. Besides pain, erosion of the teeth can be caused by their continual exposure to the acid present in gastric fluid.

Dr. Mallek is examining patients for such symptoms as changes in their teeth and soft tissues (including the pharynx), enlargement of some salivary glands, elevated levels of certain digestive enzymes, and evidence of any abnormal function of the temporomandibular joint, the hinge that connects the jaw to the temporal bone of the skull. Such studies are intended to provide dentists and physicians with new information and, ultimately, new methods for early detection of this condition.

NIDR researchers Drs. Ruth Field and Arthur Hand are studying two digestive enzymes--lingual lipase and amylase--that are important in the digestion of fats and carbohydrates. Scientists have recently discovered that these enzymes are secreted from a gland in the tongue. Using an animal model, the researchers have succeeded in purifying these enzymes--an important step in the effort to increase knowledge about their molecular properties, to characterize the secretory process in the glands, and to learn more about the function of the glands in the oral cavity.

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National Institute of Allergy and Infectious Diseases

The National Institute of Allergy and Infectious Diseases (NIAID) is conducting and supporting a wide range of studies of the gastrointestinal tract. Two diseases of major interest to NIAID are viral hepatitis and rotavirus infection.

Viral hepatitis, a potentially serious liver inflammation, is a common disease in many parts of the world. By early childhood, most people in developing countries have been infected with hepatitis A and hepatitis B viruses. About 5 percent of those infected with hepatitis B virus become long-term carriers of the virus, and approximately 25 percent of those carriers eventually develop chronic hepatitis. A close association has been reported between chronic hepatitis B infection and cirrhosis of the liver and liver cancer.

In the United States, the incidence of HBV infection is rising. Over 20,000 cases were reported in 1983, but the actual incidence is much higher, in part because hepatitis B can occur with few symptoms. An estimated 1 million Americans are chronic HBV carriers.

In 1977, scientists in Italy discovered a hepatitis-like particle in liver tissue of hepatitis B carriers. Called the delta agent, it was found to cause acute hepatitis in carriers of HBV. Delta hepatitis can also occur simultaneously with acute hepatitis B infection. The delta agent is known as a defective virus because it requires the presence of HBV for infection to occur. Recent studies carried out by Dr. John Gerin of Georgetown University, Washington, D.C., under contract with NIAID, and by NIAID intramural investigators under the direction of Dr. Robert Purcell, have further elucidated the organization and immunological properties of the delta-associated particle.

Chimpanzees that were asymptomatic chronic carriers of HBV were inoculated with the delta virus. The chimps then developed acute hepatitis. Transmission of the infection from one chimp to another was achieved, demonstrating that the delta agent is responsible for acute hepatitis in HBV carriers.

HBV is difficult to study experimentally, partly because it infects only primates. Recently, viruses resembling HBV were found to occur in other animal species. One such virus leads to acute and chronic hepatitis and liver cancer in a large proportion of eastern woodchucks in the wild. In collaboration with Dr. Gerin and Dr. Bud Tennant of Cornell University, Ithaca, New York, also under contract with NIAID, Dr. Purcell and colleagues at NIAID are studying the virology and pathology of hepatitis and liver cancer in woodchucks. The investigators are also studying maternal-fetal transmission of hepatitis in woodchucks and its relation to the development of liver cancer. They have found that woodchuck hepatitis vaccine given to newborn woodchucks can protect against perinatal transmission of hepatitis from the mother to the baby.

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In further studies, these same scientists have found that the human delta hepatitis virus can infect woodchucks suffering from chronic hepatitis. In the next few years, important information will be obtained from such studies regarding the long-term consequences of chronic hepatitis and delta virus infections in the woodchuck. This information should be useful in planning for hepatitis vaccine use in humans.

Drs. Purcell and Gerin, along with Dr. Stephen Hadler of the Centers for Disease Control and physicians in Maracaibo and Caracas, Venezuela, investigated a severe epidemic of acute hepatitis among the Yucpa Indians in rural Venezuela.

Laboratory studies of blood samples from hepatitis victims showed that the epidemic was caused either by a delta virus infection superimposed in HBV carriers or by delta infection in those experiencing acute hepatitis B infection. Virtually every patient with severe hepatitis had evidence of infection by the delta agent, whereas delta infection was rarely detected in HBV carriers living in villages where outbreaks of severe disease were not observed. Also, chronic liver inflammation was found to be unusually high among HBV carriers who had experienced delta infections compared to those with HBV infection alone. More than one-quarter of those infected by delta virus died.

Although a currently available vaccine can effectively prevent HBV infection, it is made from blood plasma of chronic HBV carriers and therefore is very expensive to produce and limited in quantity. Dr. Bernard Moss, an NIAID intramural scientist, is studying the use of vaccinia virus as a vehicle for carrying HBV genetic material that will provide immunity to hepatitis B infection. Vaccinia virus was an effective, easily administered, and inexpensive vaccine used to eradicate smallpox. Dr. Moss and his colleagues have used genetic engineering to insert HBV genes into the DNA of the vaccinia virus. They tested the vaccine in rabbits and have recently reported immunity to HBV among chimpanzees inoculated with the recombinant vaccine.

Another important vaccine is being tested for its ability to protect against rotavirus, the major cause worldwide of severe infant diarrhea. Where health care is not readily available and where poor sanitary conditions prevail, rotavirus infection results in significant infant morbidity and mortality. In the United States, as elsewhere, rotavirus infection occurs almost universally in young children. About 35 percent of young children in this country hospitalized due to dehydration from severe diarrhea have disease caused by rotavirus.

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Intramural researcher Dr. Albert Kapikian and his associates have developed an oral vaccine from the rotavirus found in rhesus monkeys. The vaccine was tested in animals and, in the last year, has been successively tested in adults, older children, and infants by NIAID-supported researchers at Vanderbilt University in Nashville, at the University of Maryland's Center for Vaccine Development in Baltimore, and at Marshall University School of Medicine in Huntington, West Virginia. Expanded clinical tests among infants and young children are continuing.

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National Institute of General Medical Sciences

The National Institute of General Medical Sciences (NIGMS) supports basic research and research training that provide the foundation for a better understanding of fundamental life processes. This research supplies new knowledge, theories, and concepts for the disease-targeted programs of other NIH Institutes.

NIGMS research programs encompass cellular and molecular biology, genetics, pharmacological sciences, and biophysics and physiological sciences. The Institute's Pharmacological Sciences Program supports research concerned with the liver's cytochrome P-450 enzyme system. This system is particularly important in drug metabolism because it helps transform foreign substances into less toxic compounds.

Dr. Milton Adesnik, an NIGMS grantee at the New York University School of Medicine, is using recombinant DNA techniques to investigate the structure and regulation of cytochrome P-450 genes. His results have contributed significantly to an understanding of the genetics of this complex system. Because much remains to be learned about digestive diseases on the cellular and molecular level, basic research such as this is crucial to advances in their treatment, prevention, and cure.

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National Institute of Child Health and Human Development

The National Institute of Child Health and Human Development (NICHD) supports a variety of research projects designed to understand events governing development of the gastrointestinal tract from fetal life to adulthood. These include studies at many levels: from the cellular processes of proliferation, differentiation, and migration, to tissue organization and function, and to organ development and functional properties. Many projects focus on methods for managing digestive and absorptive disorders in infants, children, and adolescents.

Research interests in the area of infant nutrition include the nutrient requirements of normal, premature, and growth-retarded infants, as well as analysis of human milk, cow's milk, and synthetic formulas in relation to optimal human development.

For 10 years, the NICHD has supported a major program project headed by Dr. Samuel Fomon at the University of Iowa, Iowa City. This project has developed much of the benchmark data on normal physical growth and nutritional needs during early infancy. This research group is now using stable isotopes and a new electromagnetic device that has the potential of providing useful data on the fat-free body mass of normal infants. In addition, they are assessing food consumption, energy expenditure, and growth and nutrient interactions in the management of low birth weight infants. They have found that in some soy-based formulas designed for premature infant feeding, the actual amount of calcium ingested varies considerably. In some formulas, calcium precipitates out of solution and remains in the feeding bottle.

NICHD-supported investigator Dr. Benny Kerzner at the Ohio State University College of Medicine in Columbus is studying carbohydrate metabolism in premature and newborn infants with impaired intestinal function. Glucose polymers (large molecules formed by linking glucose molecules together) provide a calorically dense, low osmolar (easier to digest) source of carbohydrate used in a number of infant formulas. Dr. Kerzner is exploring the optimum form of polymer that could be used as a carbohydrate source in the treatment of infants with gastrointestinal dysfunctions such as intractable diarrhea, short bowel syndrome, and postviral gastroenteritis. These studies will provide a better understanding of carbohydrate intolerance in infants with gastrointestinal dysfunction and a rational basis for managing them.

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The biochemical immaturity of premature infants presents challenging problems that must be solved in order to design appropriate feedings for them. For example, much has recently been learned about the complex composition of human milk and how this reflects the metabolic needs of the newborn. Milk is not just a fluid containing nutrients. It comprises a large array of substances, many of which have important nonnutritive functions.

The structure of the milk fat globule exemplifies the complicated packaging of milk components. The globule is surrounded by a membrane derived from the breast milk cell. NICHD grantee Dr. Stuart Patton at the University of California, San Diego, has recently found that this membrane has whisker-like filaments on its outer surface. Although milk from various species has been examined, so far only human milk has these structures. This observation may be important for understanding how certain enzymes called lipases can recognize milk fats for the purpose of digestion. Additionally, Dr. Patton has found that the fats in the milk-fat globule cannot be digested until the globules come in contact with bile salts in the small intestine. Thus, milk appears to contain a mechanism that prevents the digestion of its components until they reach the proper site in the digestive process.

Neonatal events impose unique adaptive needs on the gastrointestinal tract. It has been shown that a newborn child has a moderately developed intestinal tract and possesses a limited supply of energy reserves, which are stored as body fat. At birth, a complex series of secretions are released from the oral cavity, stomach, and intestine, each of which plays a critical role in digestion and absorption. Several researchers are examining the progression of the digestive processes that take place near the time of birth. The absorption of fats from the diet is critical to an infant's energy needs. Therefore, one NICHD grantee, Dr. Nicola Tavoloni at the City University of New York, has developed an animal model system to analyze bile acid secretion in the newborn. Another study by grantee Dr. Margit Hamosh at Georgetown University, Washington, D.C., is focused on the fat-digesting enzymes secreted in the mouth and in the stomach.

The intramural research program of NICHD studies metabolic diseases and disorders. A group headed by Dr. William Gahl focuses on inborn errors of metabolism with special emphasis on cystinosis. This is a genetic disease characterized by a build-up of cystine, one of the building blocks of protein. This buildup retards growth and eventually causes serious and sometimes fatal kidney damage. Dr. Gahl's research group is treating cystinotic children with a cystine-depleting agent called cysteamine (an orphan drug) as part of a national study initiated at NICHD. Cysteamine shows promise of being the first useful therapy for this serious disorder.

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In another project, Dr. James Sidbury, who studies disorders of carbohydrate metabolism, has demonstrated the usefulness of raw corn starch in the oral management of children with type I glycogen storage disease. This hereditary disease primarily affects the liver. Children afflicted with this disorder are often short in stature and have low levels of blood sugar. The usual recommended treatment for these children is frequent small carbohydrate feedings along with a high protein intake during the day and continuous overnight feeding of a high starch sugar preparation through a nasal tube. Dr. Sidbury found that eating uncooked corn starch was more effective than this regimen in meeting the dietary needs of these children. This therapy appears to stabilize blood glucose levels in patients who previously had been difficult to manage. The corn starch treatment is inexpensive, easy to manage, and eliminates the need for feeding by nasal tube throughout the night.

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Division of Research Resources

Digestive diseases are being studied extensively at General Clinical Research Centers (GCRC's). The Division of Research Resources (DRR) supports 75 GCRC's in major U.S. medical centers. Each year, scientists conduct more than 3,000 research studies in GCRC's, with more than 80 percent of the extramural inpatient research funded by NIH taking place in these centers. In addition, extensive outpatient research is also conducted.

Research in this area also receives funding from the Biomedical Research Support (BRS) program, which supports more than 9,000 pilot and regular health-related research projects at 546 institutions in the U.S. The BRS program provides a pool of flexible funds to institutions heavily involved in Public Health Service (PHS)-funded research to meet particular needs not normally covered by other grants. The funds may also complement or supplement PHS research grants by providing institutions with short-term, emergency, low-cost, interim, or shared resources.

DRR grantee Dr. Alan F. Hofmann and his colleagues at the University of California at San Diego advise patients who have had small intestine bypass surgery to restrict foods that contain oxalate--such as spinach or rhubarb--or that are rich in protein. Through mechanisms as yet unknown, cells lining the colons of these patients tend to absorb excessive amounts of oxalate. When this oxalate is later excreted with urine into the collecting ducts of the kidneys, it can combine with calcium to form stones. Dr. Hofmann conducted diet studies on a group of intestinal bypass patients at the University Hospital's GCRC. Although the results of the studies confirmed the desirability of limiting one's intake of dietary oxalate, data also implied that such an approach may fail because of other sources of urinary oxalate such as ingested protein. Dr. Hofmann speculates that creatinine, or some other constituent of protein-rich food, is converted--either by the patient's tissues or by intestinal bacteria--to a precursor of oxalate. He points out that the controlled conditions of a GCRC are necessary to conduct this type of experiment.

A new surgical procedure studied by DRR grantee Dr. Sidney F. Phillips and his colleagues at the Mayo Foundation GCRC in Rochester, Minnesota, offers the possibility of an essentially normal life style to patients who require total removal of the rectum and colon. This operation, called an ostomy, is often required for patients with severe chronic ulcerative colitis or other conditions such as colon cancer. An ostomy operation involves the removal of the anal sphincters, which are muscles that help to control a person's excretory functions. Because

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the operation causes the patient to be incontinent, the ileum must be connected to a permanent opening made in the patient's abdomen so that waste products can drain into a collection bag.

According to Dr. Phillips, the new procedure leaves the anal sphincters in place so they can function normally. The small intestine is brought through the anal sphincter region and sutured in place. A piece of the intestine is folded upon itself to form a simple reservoir, or "neorectum." Surgeons at the Mayo GCRC believe that such an operation, with careful clinical and physiological followup, will remove the need for a collection bag and save the patient from being incontinent.

Acute gastrointestinal symptoms associated with carcinoid syndrome have been partially relieved in GCRC patients at the State University of New York Downstate Medical Center in Brooklyn. Dr. Bernard M. Jaffe, a DRR grantee there, and his colleagues also report that they have developed a reliable test to diagnose this syndrome.

The carcinoid syndrome is a varied and complex group of signs and symptoms usually associated with liver metastases of carcinoid tumors. These tumors arise from specialized intestinal cells that secrete excessive amounts of serotonin, a powerful stimulant of smooth muscle contraction. Patients with carcinoid syndrome experience episodes of cutaneous flushing, diarrhea, valvular heart disease, and, less commonly, asthma. According to Dr. Jaffe, elevated plasma serotonin levels in patients with carcinoid syndrome can cause increased intestinal motility and diarrhea, but they do not seem to cause cutaneous flushing.

In a collaborative study, pentagastrin, a synthetic pentapeptide, was administered by infusion to 17 patients with carcinoid syndrome. Pentagastrin increased serotonin release and temporarily induced the characteristic signs of carcinoid syndrome (flushing, wheezing, diarrhea) in these patients, confirming that they were suffering from the syndrome. Ketanserin, an experimental serotonin receptor antagonist, greatly lessened the induced gastrointestinal symptoms when administered in a clinical research protocol. Continued treatment for 1 year with ketanserin completely stopped diarrhea in several patients. In contrast, ketanserin had little effect on cutaneous flushing.

Early administration of vitamin E may prevent development of degenerative neurologic syndrome in young children with congenital bile duct abnormalities. DRR grantee Dr. Ronald J. Sokol and his colleagues at the Children's Hospital of Cincinnati GCRC report that these abnormalities often prevent bile from reaching the small intestine and dissolving the fat-soluble vitamin E. The resulting vitamin E malabsorption leads to a

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neurologic disorder characterized by a progressive loss of eye and skeletal muscle control. These signs are usually reversible if high doses of oral or intramuscular vitamin E are administered shortly after their appearance. According to Dr. Sokol, once the neurologic signs have been established for longer periods, the likelihood of reversing the condition declines. Because neurologic injury begins during the first months of life in vitamin E deficient children, only close surveillance of a patient can detect early signs of this condition.

Scanning electron microscopy (SEM) can depict tissues in three dimensions and produces images at much higher magnifications than a light microscope. Using SEM, Dr. J. Rainer Poley, a DRR grantee at Eastern Virginia Medical School in Norfolk, examined the intestinal wall of infants suffering from soy protein intolerance. Dr. Poley found that the finger-like projections called villi, which make up the mucous membrane surface of the small intestine in healthy persons, had been destroyed in those infants with soy protein intolerance.

Because the villi absorb most of the nutrients during the digestion process, their destruction explains both the patient's chronic diarrhea and reduced ability to grow and gain weight. By using SEM, scientists may be able to better understand a variety of diseases affecting intestinal mucous membranes.

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Outlook

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases is committed to a coordinated program of basic and clinical research in digestive diseases. Highlights of the diversity and productivity of research results, attained in 1984 through Institute support, attest to the continuing progress being made both in our fundamental knowledge of digestive diseases and in the improvement of our clinical ability to deal with them. The new ideas, techniques, and research findings developed by grant-supported and intramural scientists will further the understanding of digestive disease processes and improve the treatment for those people suffering from such disorders. In the coming years preventive medicine will continue to play an ever increasing role in the Institute's research programs in digestive diseases as well as in many other disease areas under study.

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